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TWO YEARS' EXPERIENCE WITH ISONICOTINIC ACID HYDRAZIDE*

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IN MARCH 1952 isonicotinic acid hydrazide (INH) was added to the therapy in use at the Charles Camsell Indian Hospital. Up to that date we had been treating all cases of tuberculosis with interrupted courses of combined streptomycin and p-aminosalicylic acid (PAS). However, at about the same time as INH became available we also adopted the policy of long-term uninterrupted courses of streptomycin and PAS. Thus, while it became policy to place all cases of tuberculosis on streptomycin and PAS therapy, certain cases were placed on INH alone. From our experience and reports of other workers we quickly found that INH therapy given alone led to the emergence of resistant strains and the use of INH alone was abandoned, although we still maintained our original cases on INH therapy for periods up to a year. The pattern of policy soon emerged and we decided that while long-term administration of streptomycin and PAS would be the basis of all treatment, certain selected cases would have INH either added to the therapy already under way or given when PAS could not be tolerated.

Thus our criteria for the use of INH combined with streptomycin, or with streptomycin and PAS, were laid down as follows: (1) All cases of miliary tuberculosis; (2) All cases of tuberculous meningitis; (3) All cases of tuberculosis which were showing progression while on streptomycin and PAS therapy, including radiographic pulmonary spreads as well as the emergence of new lesions; (4) All cases in which sputum was not converted on streptomycin and PAS therapy after an adequate period of time (minimum 1 year); (5) All cases which could not tolerate PAS; and (6) All cases which showed toxicity on streptomycin therapy. By the end of March 1954 this group comprised 132 cases.

There were 32 patients with miliary and meningeal tuberculosis (see Table I); of these 16 are alive and well, and 16 died. This indicates at first glance a mortality of 50%. However, we wish to exclude 12 of these patients because they were in hospital two days or less and were moribund on admission. Of the four remaining, one received in error only 50 mgm. of INH instead of 250 mgm.; one died of internal hydrocephalus; one died of septic meningitis and one died of septic peritonitis. Thus, we could assume 100% survival for these cases if they had been seen early and INH used in sufficient dosage, i.e. approximately 10 mgm. per kilo. We would like to mention three special cases. Two of these cases were admitted with a diagnosis of miliary tuberculosis. They were treated with streptomycin, INH and PAS, but the dosage of INH was only 4 mgm. per kilo. At the end of three months both these patients developed tuberculous meningitis, which, however, was promptly brought under control when the dosage of INH was increased to 10 mgm. per kilo. The other case is that of a 9-month-old baby with tuberculous meningitis which was observed for a period of six weeks in a northern hospital. The clinical and laboratory data are definite. We did not expect this infant to survive. However, under a regimen of 10 mgm. per kilo. of INH and intramuscular streptomycin 0.5 gm. each day, this infant lived and gained weight and his spinal fluid returned to normal.

TABLE I.

MILIARY AND MENINGEAL TUBERCULOSIS

	Miliary	*Meningeal*	*Combined*	*Totals*
No. of patients...	7	12	13	32
No. of patients dead.....	3	3	10	16
No. of patients living.....	4	9	3	16

For the past year we have discontinued the use of intrathecal streptomycin. We regard injectable INH as essential and life-saving in infants and young children with meningitis who are vomiting.

Our experience with sputum conversion is shown in Table II. We have not attempted to analyze statistically the primary cases because it is a well-known fact that it is difficult to obtain positive cultures in young children, but in every case where we could obtain positive cultures conversion took place while on INH. Of 45 cases without sputum conversion after a year of continuous streptomycin and PAS therapy, 30 were converted when INH was added to this therapy.

*From the Charles Camsell Indian Hospital, Edmonton, Alta.

The injectable INH used in this series was supplied by Hoffmann-LaRoche, Limited.

TABLE II.

SPUTUM CONVERSION

	Strep. and PAS	*Strep., PAS and INH*
No. of cases *not* converted	45	15
No. of cases converted		30

RADIOLOGICAL FINDINGS

The following radiological observations were made. In miliary tuberculosis the miliary shadows resolved completely. It may be argued that the same thing occurred with streptomycin and PAS therapy, but we observed it to happen much more rapidly with INH. We saw definite improvement in one month, and certainly cases of miliary tuberculosis which were doing badly on streptomycin and PAS improved rapidly with the addition of INH to therapy. Of the moderately advanced and far advanced cases, there were 29 which had radiographic evidence of spread on streptomycin and PAS alone. The addition of INH resulted in rapid disappearance of the exudative element and then the slower retraction and fibrosis of the productive element. In the pneumonic lesions changes were noted within a month and disappearance of the exudative element in three months. In 50 pulmonary cases with cavities we saw only one case in which we could say the cavity closed; in three the cavity became smaller. In one case a 1 cm. cavity was converted into a solid lesion. Thus we were not impressed by the effect of INH on cavity closure. The solid lesions were apparently unaffected by INH therapy.

EXTRAPULMONARY LESIONS

There were ten cases in which extrapulmonary lesions developed while on streptomycin and PAS (Table III). These lesions healed when INH was added to therapy. There were eight genito-urinary lesions. In two of these conversion took place on streptomycin and PAS, but in the other six it did not occur, even on long-term streptomycin and PAS, until INH was added to therapy.

TABLE III.

EXTRAPULMONARY LESIONS WHICH DEVELOPED DURING STREPTOMYCIN AND PAS TREATMENT

Lesion	*No. of cases*
Mediastinal adenitis	3
Epididymitis	1
Bone lesion	2
Pleurisy	1
Mastoiditis	2
Meningitis	1

There were 12 patients with 14 bone lesions. All had INH added to therapy because of a failure of response to streptomycin and PAS. Of these 12, three developed a new or second bone lesion, eight had progression of bone or joint lesions and there were five related sinuses which did not close on streptomycin and PAS therapy. In 11 of these individuals the lesion became stable when INH was added and four of the sinuses closed. A spine lesion and an elbow lesion became inactive and later showed radiographic evidence of fusion after INH was added. The twelfth case, with a spine lesion, was treated with streptomycin and PAS because the sputum remained positive. INH was added and the bone lesion thereupon improved radiographically.

We had two cases of tuberculous peritonitis. In one, a young boy was admitted following an attempted paracentesis of the abdomen; operation revealed a tuberculous peritonitis with a ruptured viscus. After a very stormy course this boy recovered and did well. He was treated with streptomycin and INH in a dosage of 10 mgm. per kilo. The other patient was an acutely ill young woman with a large mass filling the abdomen. After initial therapy with streptomycin and INH her abdomen was drained, and the diagnosis of tuberculous peritonitis confirmed. We are of the opinion that both these patients would have died without INH therapy.

DEATHS

Of the 132 patients 18 died, 15 deaths being due to miliary and meningeal tuberculosis. Of the 15, 12 were in hospital less than two days and were moribund on admission. Three were in hospital 1-3 months but each presented a special problem. The first one was an adult with pulmonary and genito-urinary disease. He had a thoracoplasty, following which he developed meningitis. In error he received only 50 mgm. of INH per day.

The second was a case of meningitis in which ventricular block developed early. Burr holes were made and intraventricular streptomycin was used. However, he actually died of a staphylococcal meningitis.

Canad. M. A. J.
April 1, 1955, vol. 72

TABLE IV.

17-KETOSTEROID VALUES DURING INH THERAPY

Name	*Sex*	*Age*	*17 K.S.*	*Creatinine*	*Normal K.S.**	*Interpretation*
F.M.	M.	9 years	2.66 ± 0.4	0.36	0.23–2.30	N.
M.I.	F.	11 years	3.33 ± 0.5	0.53	0.23–2.30	S.E.
R.G.	M.	7 years	2.53 ± 0.38	0.47	0.26–1.55	S.E.
G.H.	M.	6 years	1.14 ± 0.17	0.28	0.26–1.55	N.
F.B.	M.	8 years	1.40 ± 0.21	0.55	0.26–1.55	N.
S.C.	F.	9 years	3.53 ± 0.58	0.42	0.23–2.30	S.E.
F.R.	M.	7 years	4.79 ± 0.72	0.69	0.26–1.55	M.E.
		Repeat determination after withdrawal of INH for 10 days				
F.R.	M.	7 years	3.54 ± 0.52	0.62	0.26–1.55	M.E.
R.G.	M.	7 years	2.25 ± 0.34	0.61	0.26–1.55	S.E.

*Wood and Gray, *J. Endocrinology*, 6: 111, 1949.
Interpretation code: N.—Normal
S.E.—Slightly elevated
M.E.—Moderately elevated

The third was a girl with an early ventricular block. Burr holes were made and intraventricular streptomycin was started, but the block was not relieved and she died of extreme internal hydrocephalus. Autopsy did not reveal any active meningitis.

Of the remaining three patients one was a man who died of acute cardiac failure two months after discharge. The second was a boy admitted after an appendectomy. Our diagnosis was tuberculous meningitis, proved by guinea-pig inoculation. He did well on treatment and then suddenly died. The pathologist could find no evidence of tuberculosis and gave the cause of death as septic peritonitis with heart failure. The third had spontaneous pneumothorax and died in the first 24 hours. We have critically analyzed these deaths because we believe that none of them shows direct evidence of INH failure in therapy.

KETOSTEROID VALUES

17-Ketosteroid determinations were carried out on seven children in this group with tuberculosis in various forms. Their ages ranged from six to 10 years. According to the standard used by our university hospital biochemical laboratory, the values were definitely increased.

Two children were then taken off INH for a period of 10 days, and 17-ketosteroid determination repeated. The results were still increased. We offer no interpretation of these results, as we believe that determinations would have to be made on a larger number of children of comparable age and race with comparable disease in order to arrive at a set of normal values. Our results are shown in Table IV.

SUMMARY

1. A group of 132 tuberculous patients have been given intramuscular streptomycin, PAS and INH therapy.

2. When INH is added to streptomycin and PAS the mortality in tuberculous meningitis and/or miliary tuberculosis should approach zero, provided the patient is seen reasonably early and the INH is used up to a level of 10 mgm. per kilo.

3. Injectable INH is life-saving in young children and infants who are vomiting.

4. The basis of all tuberculosis therapy should be streptomycin and PAS.

5. It is not necessary to use intrathecal streptomycin.

6. The statement that tuberculous meningitis does not appear when the patient is under treatment with streptomycin and INH is erroneous unless the INH is used at a level of 10 mgm. per kilo., as in our series.

7. INH should be reserved for meningitis and miliary tuberculosis; for cases which become resistant to streptomycin; for cases which do not show sputum conversion; for cases undergoing surgery which have not responded to streptomycin and PAS, and for cases of spread while on streptomycin and PAS.

8. The addition of INH is of particular value in speeding the healing of sinuses related to bone and joint disease.

9. INH is of great value where a patient cannot tolerate PAS, particularly in pregnancy.

10. The addition of INH is of particular value in genito-urinary cases.

11. Few toxic signs of INH therapy were seen and in no case was therapy discontinued.